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10/035,637	11/07/2001	Yashwant M. Deo	CDJ-166CP	4452

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EXAMINER	
EWOLDT, GERALD R	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/035,637	DEO ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/22/06 and 2/16/07*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-35,38.39,42-46 and 51-56* is/are pending in the application.

4a) Of the above claim(s) *42-46 and 53-56* is/are withdrawn from consideration.

5)☒ Claim(s) *31* is/are allowed.

6)☐ Claim(s) *27-30,32,33,38,39,51 and 52* is/are rejected.

7)☒ Claim(s) *34 and 35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments, remarks, declaration of Inventor Kelor, new Abstract, new Title, amended drawing, substitute CRF and Sequence Listing, and IDS, filed 11/22/06 and 2/16/07, have been entered.

2. Claims 42-46 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions. New Claims 53-56 are drawn to molecular conjugates comprising patentably distinct species. Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, Claims 53-56 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 27-35, 38, 39, 51, and 52 read on the elected invention and are being acted upon.

3. The new Title and Abstract, amended drawing, substitute CRF and Sequence Listing are acceptable.

4. As set forth previously, The instant application claims priority to Application Nos. 09/851,614, 60/203,126, and 60/230,739. A review of the '614 application shows that the molecular conjugate of said application is not the molecular conjugate of the instant claims. The conjugate of the '614 application, as recited in Claims 1 and 5, is "specific" for DCs; the conjugate of the instant claims does not include this limitation. Additionally, the conjugate of the '614 applications comprises additional limitations, also set forth in claim 1:
a) a binding affinity constant to a dendritic cell of at least about 10^7 M^{-1};
b) the ability to opsonize a dendritic cell;
c) the ability to internalize after binding to dendritic cells; or
d) the ability to activate dendritic cells.
Accordingly, priority to the '614 application is denied. The priority date of the instant application is its filing date, 11/07/01.

Applicant argues that the molecular conjugate of the instant claims is indeed disclosed in the '614 application.

A review of the '614 application reveals that molecular conjugates are disclosed at just two cites in this jumbo specification. At page 37 the specification discloses Antibody Conjugates/Immunotoxins. Clearly, these are not the molecular conjugates of the instant claims comprising antigens. The second cite is at page 47 of the specification. Here the

specification discloses a molecular complex "comprising at least one binding specificity for a component on the surface of a dendritic cell linked to an antigen". It is the Examiner's position that the disclosure is in the context of a conjugate specific for a DC and not the context of the claim wherein the conjugate binds the human macrophage mannose receptor (hMMR).

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 27-30, 32, 33, 38, 39, 51, and 52 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,922,845 (IDS) in view of Tuting et al. (1998, of record) and Sallusto et al. (1995).

As set forth previously, The '845 patent teaches a molecular conjugate comprising an antibody that binds to dendritic cells (DCs) (FcαR) and an antigen, wherein said antigen comprises a component of a pathogen or a tumor (cancer) antigen (see column 3, lines 49-59). The reference further teaches the conjugate comprising a single chain antibody (see column 3, line 63), a pharmaceutically acceptable carrier (see column 4, line 32), and an adjuvant (see column 21, line 54. The reference further teaches that the molecular conjugates of the reference can be used to "harness the capabilities of white blood cells", e.g., phagocytosis, for "enhancing the attack of these cells against cancer cells, cells of infectious microorganisms, and cells infected with pathogens".

The reference teaching differs from the claimed invention only in that it does not teach a molecular conjugate comprising an antibody that binds to a human macrophage mannose receptor and the Pmel-17 tumor antigen.

Tuting et al. teaches that Pmel-17 is one of several well known melanoma antigen (see particularly page 1140, column 1).

Sallusto et al. teaches that the human mannose macrophage receptor (which would be encoded by SEQ ID NO:7) can be employed for the uptake of antigen by DCs for presentation of said antigen to T cells (see particularly Abstract; page 392, column 1; and Figure 4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to produce a molecular conjugate comprising an antibody that binds to white blood cells (which would include DCs) and tumor antigen, as taught by the '845 patent, employing an antibody that binds the human macrophage mannose receptor and Pmel-17 as the antigen. One of ordinary skill in the art at

the time the invention was made would have been motivated to employ an antibody that binds the human macrophage mannose receptor because it is more APC-specific than is the FcαR of the '845 patent, thus allowing for more efficient antigen uptake by APCs and more efficient antigen presentation to T cells. One of ordinary skill in the art at the time the invention was made would have been motivated to employ any of the well known tumor antigens in an anti-cancer therapeutic agent, such as Pmel-17 as taught by Tuting et al., because of their availability and previous characterization.

Applicant's arguments, filed 3/30/06, have been fully considered but they are not persuasive. Applicant argues that mAb bind targets with high affinity and such antibodies would not have been thought suitable for targeting antigens to the mannose receptor because the antigen-antibody complex would fail to dissociate upon internalization.

First note that Applicant has provided no evidence that the skilled artisan would not have expected the antigen-antibody complex to dissociate upon internalization, but regardless, the skilled artisan would have simply selected an antibody with reduced binding affinity if this were a concern.

Applicant argues, "Sallusto et al. make a clear distinction between mannose receptor mediated-endocytosis of ligands and the internalization of Fc receptors and their ligands; the latter of which results in delivery to lysozomes and the degradation of both the ligand and the receptor. Accordingly, one of ordinary skill would not have been motivated to have used antibodies to target antigens to dendritic cells since such antibodies would have been expected also to bind the Fc receptors expressed on these cells, thus, resulting in degradation of the ligand and the receptor".

Again the arguments comprises only an attorney's perception of a potential problem. Regardless, the skilled artisan could have simply overcome this potential problem by using more conjugate or selecting an antibody of appropriate binding affinity, i.e., an affinity slightly higher than the affinity of the FcR for the Fc region of an antibody.

Applicant discusses macropinocytosis and speculates that "such mechanisms … would not have been thought suitable for antibody-based vaccines".

Again, Applicant provides only an attorney's speculation.

Applicant cites Ramakrishna et al. (2004) wherein the use of an antibody to target antigens to the mannose receptor, i.e., the method of the instant claims is taught. Interestingly, it is noted that the lead Inventor, Yashwant Deo, is not included as an author of the paper, but the remaining Inventors, Keler, Treml, and Endres are. Regardless, a review of the work shows that the authors never indicate that the construction and use of a molecular conjugate for the targeting of antigens to the mannose receptor is anything other than routine. They do not indicate anything unexpected, surprising, nor particularly difficult in producing a functional conjugate. Indeed, they indicate that they are simply employing the same rationale used by Steinman et al. wherein the related DEC-205 receptor was targeted for the introduction of antigen into DCs.

Applicant's arguments, filed 216/07, have been fully considered but they are not persuasive. Applicant argues that the hMMR would not have been considered to be suitable for

antibody-mediated antigen targeting and cites the declaration of Inventor Keler.

The Inventor's declaration will be considered here.

The Inventor asserts a number of reasons for why the hMMR might not allow for the internalization and release of an antigen by a DC. The Inventor concludes with the opinion that, "there would not have been motivation to have made the presently claimed molecular conjugates comprising a human monoclonal antibody that binds to the human macrophage mannose receptor linked to an antigen". The Inventor also notes that the antibody of Sallusto et al. blocked the hMMR.

In view of the record as a whole, the Inventor's opinion is not found to be persuasive. As set forth previously, when the Inventors published the work of the instant specification they simply stated that they were following the previously taught methods of Steinman et al. wherein the related DEC-205 receptor was targeted for the introduction of antigen into DCs. There was no teaching by the instant Inventors that they encountered any particular difficulties or produced any unexpected results. Also, it must be noted that the specification fails to disclose what distinguishes an antibody that blocks the MMR from an antibody that facilitates entry through the MMR. If the Inventor's argument were to be found to be persuasive, then it would be *absolutely critical* to the claimed genus of conjugates that said distinction be addressed. As it has not been addressed in the instant specification, indeed it appears that the Inventors simply produced the B11 antibody of SEQ ID NOS:2 and 4 (and it worked), the specification could not be enabling for the genus of claimed conjugates.

In the instant remarks Applicant continues to argue a lack of expectation of success.

Again, the Examiner finds this line of argument curious. Applicant is surely aware that unexpected results apply only to the specific invention for which the unexpected results have been demonstrated. Unexpected results *cannot* be applied generically. Absent an expectation of success the generic conjugate of the instant claims *cannot* be found to be allowable. It appears then that Applicant is arguing against his own generic invention. As the specification discloses just a single example of an antibody that could function in the instant

molecular conjugate (the B11 antibody), and said antibody has been allowed, it is unclear to the Examiner what possible outcome is expected from this line of argument.

7. Claims 27-30, 32, 33, 38, 39, 51, and 52 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2002/0187131 (IDS) in view of U.S. Patent No. 5,922,845 (IDS), and Tuting et al. (1998), all of record.

As set forth previously, The '131 application discloses a molecular conjugate (including recombinant and chemically conjugated), comprising an antibody (including a single chain antibody) and an antigen (including tumor or pathogen antigens), see particularly paragraphs 19, 20, 43, and 46.

The reference teaching differs from the claimed invention only in that it does not teach a molecular conjugate comprising a human monoclonal antibody and the Pmel-17 tumor antigen.

Tuting et al. and the '845 patent have been discussed above. The '845 patent further teaches the value of molecular conjugates comprising human monoclonal antibodies including the elimination of a HAMA (human anti-mouse antibody) response, see particularly column 8, line 33 - column 9, line 33).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to produce the molecular conjugate of the '131 application comprising the Pmel-17 tumor antigen and a human monoclonal antibody. One of ordinary skill in the art at the time the invention was made would have been motivated to employ the Pmel-17 as taught by Tuting et al., because of its availability and previous characterization, and a human monoclonal antibody, as taught by the '845 patent for the elimination of a HAMA response.

Applicant echoes the arguments set forth in response to the previous rejection.

See the Examiner's response in section 6 above.

8. The following is a new grounds of rejection necessitated by Applicant's amendment.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 32 is rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the molecular conjugate comprising SEQ ID NOS:2 and4 and a generic melanoma antigen.

Applicant cites no support in the specification for the claimed conjugate.

Applicant is advised that a review of the specification revels no specific support for the specific antibody construct of SEQ ID NOS:2 and 4 linked to any generic melanoma antigen.

11. Claim 31 is allowed. Claims 34 and 35 would be allowable if recited in independent form.

12. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

14. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

5/5/07

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